



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification³ : A61K 7/06	A1	(11) International Publication Number: WO 85/ 04577 (43) International Publication Date: 24 October 1985 (24.10.85)
(21) International Application Number: PCT/US85/00556 (22) International Filing Date: 2 April 1985 (02.04.85) (31) Priority Application Numbers: 597,252 624,758 (32) Priority Dates: 6 April 1984 (06.04.84) 26 June 1984 (26.06.84) (33) Priority Country: US (60) Parent Application or Grant (63) Related by Continuation US 624,758 (CIP) Filed on 26 June 1984 (26.06.84) (71)(72) Applicant and Inventor: BAZZANO, Gail, Sansone [US/US]; 4506 Avron Boulevard, Metairie, LA 70002 (US).		(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
(54) Title: COMPOSITIONS USED FOR HAIR GROWTH		
(57) Abstract The use of substituted pyrimidines designated as compounds A, B, C, D, series and methyl 5-<3, 6-dihydro-1(2H)-pyridyl>-2-oxo-2H-<1, 2, 4>oxadiazolo<2, 3, - α >pyrimidine-7-carbamate and their active derivatives and analogs and combinations of these with retinoids to increase the rate of hair growth and to prolong the anagen phase of the hair cycle and to treat certain types of alopecia.		

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COMPOSITIONS USED FOR HAIR GROWTH
Description

Brief Summary of the Invention:

Methyl 5-<3, 6-dihydro-1(2H)-pyridyl>-2-oxo-2H-<1, 2, 4> oxadiazolo<2, 3, -α> pyrimidine-7-carbamate and Compounds A, B, C, D, E, F, series and their active derivatives and analogs, when applied topically to the skin of mammals, or administered orally, stimulate or improve the rate of hair growth and they exhibit effectiveness in the treatment of alopecia. Furthermore, retinoids and analogs, and mixtures of these compounds with Compounds A, B, C, D, series and methyl 5-<3, 6-dihydro-1(2H)-pyridyl>-2-oxo-2H-<1, 2, 4>oxadiazolo<2, 3, -α>pyrimidine-7-carbamate and their active derivatives and analogs, when applied topically to the skin of mammals, or administered orally, stimulate or improve the rate of hair growth and they exhibit effectiveness in the treatment of alopecia.

Related Applications:

This application is related in part to application serial U.S. 235,169, filed February 17, 1981; application serial U.S. 318,607, filed November 9, 1981; application serial U.S. 386,730 filed June 9, 1982, and application serial U.S. 414,854 filed September 3, 1982. The compounds claimed in this application are disclosed in applications and patents listed as follows: German Offen. 2,804,518, filed August 17, 1978; U.S. Patents 4,220,772 and 4,256,886; German Offen. 2,804,519, filed August 10, 1978; Swiss Applic. 78/7,910, filed July 21, 1978; Helvetica Chimica Acta Vol. 65 Fasc. 5 (1982), pp. 1445-1467, Helvetica Chimica Acta Vol. 66 Fasc. 2 (1983), pp. 669-672; U.S. Patents 4,150,131 and 4,360,521, and Belgium patent No. 893,833, filed January 14, 1983 and CH application 81/4,640, filed July 15, 1981.

Background of the Invention:

The present invention relates to topical application of Compounds A, B, C, D, series and methyl 5-<3, 6-dihydro-1(2H)-pyridyl>-2-oxo-2H-<1, 2, 4> oxadiazolo 2,3,-α> pyrimidine-7-carbamate and their active analogs and derivatives for improving the rate of hair growth on mammalian skins and for the treatment of alopecia, as well as the use of the forementioned compounds and their analogs with retinoids.

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A normal characteristic of hair growth in mammals, including human, is that in most cases the rate of hair growth and the length of its growth cycle are reduced with age. These phenomena are common to all mammals with rare exceptions and they must be differentiated from true male pattern alopecia.

United States Patent No. 4,139,619 issued to Charles A. Chidsey on February 13, 1979 discloses a process for stimulating the growth of mammalian hair by topical application of certain preparations containing, as the active ingredient, 6-amino-4 (substituted amino)-1,2-dehydro-1-hydroxy-2-iminopyrimidine. This patent further states that the active compounds and the methods of their preparations are disclosed in United States Patent No. 3,461,461, which was issued on August 12, 1969. Most examples in the patent to Chidsey describe various preparations such as topical cream, topical ointment, solution, aerosol and dusting powder, and state that these preparations can be applied to the bald human scalp to stimulate the rate of growth of terminal hair.

International Application Numbers PCT/US81/00338 and PCT/US82/01593 by applicant Gail Bazzano disclose chemical compositions containing retinoids and minoxidil which can be used to increase the rate of growth of hair and to treat alopecias.

It is the object of the present invention to provide additional compositions or preparations which are effective in improving the rate of hair growth on mammalian skin, as described and listed on Pages 9,10,11 of this patent application.

It is also the object of this invention to provide such compositions for topical applications to mammalian skin, in combination with retinoids, in order to stimulate or improve the rate of hair growth thereon and to prolong the anagen phase of the hair cycle.

The foregoing and other objects and advantageous features of this invention will be more clearly comprehended from the following detailed description.

Detailed Description of the Invention:

It has been unexpectedly discovered that the subject compounds, when applied to a mammalian skin, in an effective amount, stimulate or improve the rate of hair growth and prolong the anagen phase of the hair cycle. Moreover, these compounds have also been found to be effective in treatment of alopecia. Typically, these compounds constitute the active

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ingredients of different types of preparations such as lotions, solutions, ointments, creams, sprays and the like.

The compounds of the present invention which form the active ingredients in the hair treatment preparations include Compounds A, B, C, D, series and methyl 5-<3, 6-dihydro-1(2H)-pyridyl-2-oxo-2H-<1, 2, 4>oxadiazolo<2, 3- α

Suitable retinoid active ingredients for use in this invention include derivatives of retinoic acid which have been described in PCT applications: U.S. 81/00338 and U.S. 82/01593.

Preparations such as lotions, creams, conditioners, and the like, including the aforementioned compounds as the active ingredients, can be applied topically to the skin for stimulating or improving the rate of hair growth. It has surprisingly been discovered that the compounds of the present invention, in comparison with minoxidil, when applied topically to the skin have excellent penetration and a long lasting effect, in producing hair growth in an animal model for androgenetic alopecia. Furthermore, retinoids in combination with the subject compounds of this application exhibit synergism in the animal model studied.

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As used herein, the term retinoid denotes retinol, retinal, retinyl esters as well as retinoic acid and its esters, amides, derivatives, analogs and metabolites. As described in PCT U.S. 82/01593, the terminal groups may be oxidized, reduced, esterified, etc. The alkali metal (sodium, potassium, etc.) and alkaline earth metals (magnesium, zinc, calcium, etc.) salts of these compounds are also included herein.

The pharmaceutical, cosmetic or veterinary preparations of the present invention can be prepared by conventional techniques for the preparation of lotions, creams, conditioners or shampoos for the scalp or veterinary preparations for pelis. Included also are preparations which can be administered orally and compounds which can be added to animal foods.

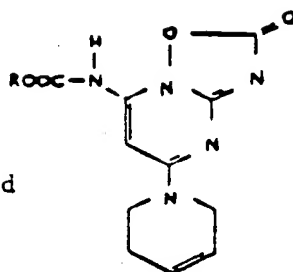
In addition to the active compounds of this invention, the various preparations can contain any conventional pharmaceutically acceptable or cosmetically acceptable inert or pharmacodynamically active additives or carriers. For example, the lotions may be prepared using various forms of alcohols or other solubilizers such as glycols, or esters. The conditioners may contain the normally acceptable commercially produced compounds such as cetyl alcohol, ceteareth-5, -20 hydrantoin, hydrolyzed animal protein, glycol stearate, amodimethicone, paraffin, mineral oil, etc. The topical compounds may also contain various oils including essential fatty acids and phospholipids and other polyunsaturated fatty acids and their derivatives and prostaglandins and prostacyclins and their derivatives and analogs and other compounds which can be vasodilators, vitamins or hormones.

The topically applied lotions, creams, and conditioners, etc., will vary according to the standard art with regard to the amounts of other hydrophilic and hydrophobic containing ingredients, including emulsifiers, so that either an oily, semi-oily or oil-free product may be obtained. The shampoos may contain any of the conventionally used detergents or soaps and any other compounds used by those familiar with the art. Oil-based shampoos are included in these formulations.

The topical treatments may consist of lotions, creams, conditioners, shampoos, oil treatments, etc., with from 0.001 to 5% by weight of the active ingredients, Compounds A, B, C, D, series and all-trans retinoic acid or derivatives, or other retinoids, as the preferred dosages in these compositions.

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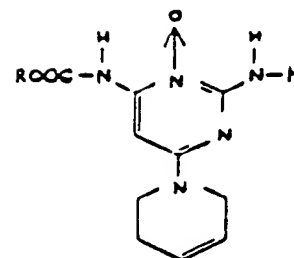
Compound
A



methyl-5-[3,6-dihydro-1(2H)-pyridyl]
-2-oxo-2H-[1,2,4]-oxadiazolo[2,3-a]
pyrimidine-7-carbamate

R=methyl

Compound
B



methyl 2-amino-6-[3,6-dihydro-1
(2H)-pyridyl]-4-pyrimidine car-
bamate-3-oxide

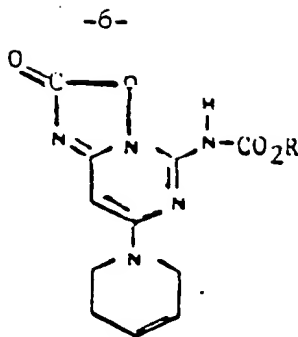
R=methyl

R can be equal to :

- a methyl
- b ethyl
- c butyl
- d *i*-butyl
- e benzyl
- f 2-methoxy-ethyl

R can be equal to .:

- a methyl
- b ethyl
- c butyl
- d *i*-butyl
- e benzyl
- f 2-methoxy-ethyl

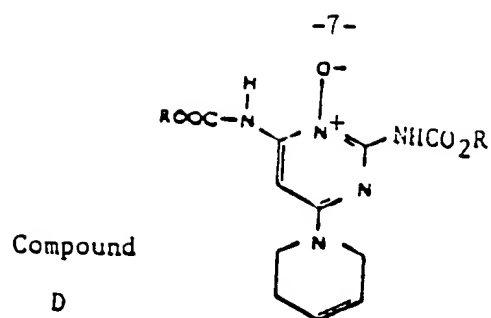


Compound
C

methyl-5-[3,6-dihydro-1(2H)-pyridyl]
-2-oxo-2H-[1,2,4]-oxadiazolo[2,3-l]
pyrimidine-7-carbamate R=methyl

R can be equal to a) methyl, b) ethyl, c) butyl, d) *i*-butyl,
e) methoxy ethyl or f) allyl

R	Np. (dec.) [°C]	Molecular formula
a methyl	215	C ₁₂ H ₁₃ N ₅ O ₄ 291.27
b ethyl	202-204	C ₁₃ H ₁₅ N ₅ O ₄ 305.30
c butyl	197-198	C ₁₅ H ₁₉ N ₅ O ₄ 333.35
d <i>i</i> -butyl	197-198	C ₁₅ H ₁₉ N ₅ O ₄ 333.35
e methoxy-ethyl	203-204	C ₁₄ H ₁₇ N ₅ O ₅ 335.32
f allyl	207-209	C ₁₄ H ₁₅ N ₅ O ₄ 317.31



dimethyl-6-[3,6-dihydro-1(2H)-pyridyl]-2,4-
pyrimidine dicarbamate-
3-oxide

R can be equal to a) methyl, b) ethyl, c) butyl, d) *i*-butyl,
e) benzyl, or f) 2-methoxy ethyl

4	R	Mp. [°C]	Molecular formula
a	methyl	202-206	C ₁₃ H ₁₇ N ₅ O ₅ 323.309
b	ethyl	154-155	C ₁₅ H ₂₁ N ₅ O ₅ 351.363
c	butyl	131-132	C ₁₉ H ₂₉ N ₅ O ₅ 401.471
d	<i>i</i> -butyl	137-139	C ₁₉ H ₂₉ N ₅ O ₅ 401.471
e	benzyl	172	C ₂₅ H ₂₅ N ₅ O ₅ 475.505
f	2-methoxy-ethyl	126-128	C ₁₇ H ₂₅ N ₅ O ₇ 411.415

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Example ITopical Lotion

<u>Components</u>	<u>Weight %</u>
Active Ingredient:	
Compound A methyl-5-[3,6-dihydro-1(2H)-pyridyl] -2-oxo-2H-[1,2,4]-oxadiazolo[2,3-a] pyrimidine-7-carbamate	1.0
Active ingredient: All-trans retinoic acid	0.1
Ethanol	q.s. to 100.0
Propylene glycol	5.0
Butylated hydroxytoluene	0.1
Safflower oil	1.0
2-tocopherol acetate	0.5

Example IITopical Cream Conditioner

<u>Components</u>	<u>Weight %</u>
Active Ingredient:	
Compound B methyl 2-amino-6-[3,6-dihydro-1 (2H)-pyridyl]-4-pyrimidine car- bamate-3-oxide	5.0
Active ingredient: Retinoic Acid	0.1
Distilled Water	q.s. to 100.0
Cetrimonium Chloride	5.0
Cetyl alcohol	4.0
Ethanol	84.0
Butylated hydroxytoluene	1.0
Hydrolyzed animal protein	0.5
Methylparaben, propylparaben	0.1

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Example III

3.0 grams of Compound A (methyl-5-[3,6-dihydro-1(2H)-pyridyl]-2-oxo-2H-[1, 2, 4]-oxadiazolo[2,3-a] pyrimidine-7-carbamate) and 0.1 grams of 13-cis retinoic acid is dissolved in 10 ml. of acetone, and the solution admixed with 90 grams of USP grade hydrophilic ointment to a uniform consistency, one gram of butylated hydroxytoluene is then added to this mixture. The water washable cream ointment thus prepared consists of 0.1% retinoic acid ingredient and 3% of Compound A (methyl-5-[3,6-dihydro-1(2H)-pyridyl]-2-oxo-2H-[1,2,4]-oxadiazolo[2,3-a] pyrimidine-7-carbamate).

Example IV

<u>Lotion Formulation for the Topical Administration</u>	<u>Weight %</u>
Active Ingredient:	
Compound D ₁ methyl-5-[3,6-dihydro-1(2H)-pyridyl] -2-oxo-2H-[1,2,4]-oxadiazolo[2,3-a] pyrimidine-7-carbamate	1.0
Active ingredients: Retinoic Acid	0.1
Ethanol	q.s. to 100.0
Propylene glycol	5.0
Butylated hydroxytoluene	0.1
Safflower oil	1.0
α -tocopherol acetate	0.5
Stabilizer	0.1

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Example VCream Conditioner for Topical Administration

Active Ingredient:

Compound D dimethyl-6-[3,6-dihydro-1(2H)-

pyridyl[-2,4-pyrimidine dicarbamate-

3-oxide

Weight %

5.0 to 1.0

Active ingredients: Retinoic Acid

0.1

Distilled Water

q.s. to 100.0

Cetrimonium Chloride

5.0

Cetyl alcohol

4.0

Ethanol

84.0

Butylated hydroxytoluene

1.0

Hydrolyzed animal protein

0.5

Methylparaben, propylparaben

0.1

Stabilizer

0.1

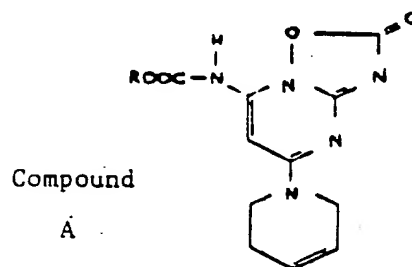
The aforementioned examples are only examples and are not meant to be limiting.

SUBSTITUTE SHEET

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Claims

1. A composition useful for increasing the rate of hair growth on mammalian skins, prolonging the anagen phase of the hair cycle and for treating various types of alopecias, comprising an effective amount of a compound selected from the series consisting of Compound A: methyl-5-[3,6-dihydro-1(2H)-pyridyl]-2-oxo-2H-[1,2,4]-oxadiazolo[2,3-a]pyrimidine-7-carbamate and its active analogues, as described below.



methyl-5-[3,6-dihydro-1(2H)-pyridyl]
-2-oxo-2H-[1,2,4]-oxadiazolo[2,3-a]
pyrimidine-7-carbamate

R=methyl

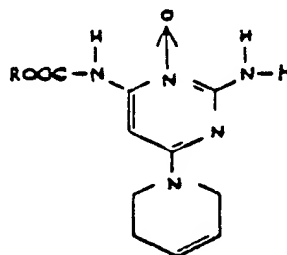
R can be equal to :

- a methyl
- b ethyl
- c butyl
- d *i*-butyl
- e benzyl
- f 2-methoxy-ethyl

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2. A composition useful for increasing the rate of hair growth on mammalian skins, prolonging the anagen phase of the hair cycle and for treating various types of alopecias, comprising an effective amount of a compound selected from the series consisting of Compound B: methyl-2-amino-6-[3,6-dihydro-1(2H)-pyridyl]-4-pyrimidine carbamate-3-oxide and its active analogues, as described below.

Compound
B



methyl 2-amino-6-[3,6-dihydro-1
(2H)-pyridyl]-4-pyrimidine car-
bamate-3-oxide

R=methyl

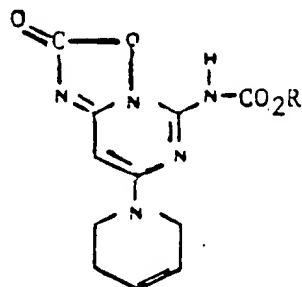
R can be equal to :

- a methyl
- b ethyl
- c butyl
- d *i*-butyl
- e benzyl
- f 2-methoxy-ethyl

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3. A composition useful for increasing the rate of hair growth and mammalian skins, prolonging the anagen phase of the hair cycle and for treating various types of alopecias, comprising an effective amount of a compound selected from the series consisting of Compound C: methyl-5-[3,6-dihydro-1(2H)-pyridyl-2-oxo-2H-[1,2,4]-oxadiazolo[2,3-1]pyrimidine-7-carbamate, as described below.

Compound
C

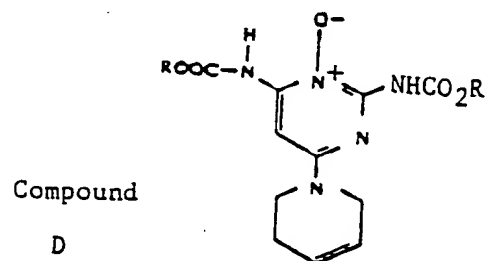


methyl-5-[3,6-dihydro-1(2H)-pyridyl]
-2-oxo-2H-[1,2,4]-oxadiazolo[2,3-1]
pyrimidine-7-carbamate

R can be equal to: a) methyl, b) ethyl, c) butyl, d) *i*-butyl,
e) methoxy ethyl f) allyl

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4. A composition useful for increasing the rate of hair growth on mammalian skins, prolonging the anagen phase of the hair cycle and for treating various types of alopecias, comprising an effective amount of a compound selected from the series consisting of Compound D: dimethyl-6-[3,6-dihydro-1(2H)-pyridyl]-2,4-pyrimidine dicarbamate-3-oxide and its active analogues, as described below.



dimethyl-6-[3,6-dihydro-1(2H)-pyridyl]-2,4-
pyrimidine dicarbamate-
3-oxide

R can be equal to a) methyl, b) ethyl, c) butyl, d) *i*-butyl
e) benzyl or f) 2-methoxy ethyl

5. A composition useful for improving the rate of hair growth on mammalian skins which comprises topically applying to the skin an effective amount of a compound selected from the group consisting of retinoid, analogs and Compounds A, B, C, or D series or methyl 5-<3, - $\alpha\alpha$

6. A composition of Claim 5 wherein the retinoid is selected from the group consisting of stereoisomers of vitamin A acid as well as the aldehydes, alcohols, esters, amides, ethers and salts of said compounds, or a retinoid analog, such as those listed in PCT U.S. 82/01593.

INTERNATIONAL SEARCH REPORT

International Application No. **PCT/US85/00556**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ¹

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl. **(3) A61K 7/06**

U.S. Cl. **70**

II. FIELDS SEARCHED

Minimum Documentation Searched ⁴

Classification System

Classification Symbols

U.S. **424/70**

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched ⁵

BAZZANO, GAIL SANSONE

III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴

Category ⁶	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
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A	US, A, 4,129,662, Gander, 12 December, 1978	1
A	US, A, 4,190,594, Gander, 26 February, 1980	1
X	N, FDA CONSUMER, February, 1981, Vol. 15, No. 1, See pages 10 and 12	1 to 7

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IV. CERTIFICATION

Date of the Actual Completion of the International Search ¹

06/07/85

Date of Mailing of this International Search Report ¹

21 JUN 1985

International Searching Authority ¹

ISA/USA

Signature of Authorized Officer ¹⁰

Dale R. One

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